UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/851,089	07/07/97	DARZINS	A

HM11/0608

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ART UNIT	PAPER NUMBER
1652	5

DATE MAILED: 06/08/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/851,089	Darzins et al.
Examiner	**Group Art Unit**
Einar Stole	1652

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-75* is/are pending in the application.

Of the above, claim(s) *1 and 54-75* is/are withdrawn from consideration.

☒ Claim(s) *9-23 and 40-45* is/are allowed.

☒ Claim(s) *2-8, 24-39, and 46-53* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims *1-75* are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 6

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Claims 1-75 are presented for examination.

Election/Restriction

2. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claim 1, drawn to a *Sphingomonas* culture, classified in class 435, subclass 243.

II. Claims 2-53, drawn to oxidoreductases, nucleic acids encoding these enzymes, and vectors and transformed host cells thereof, classified in class 435, subclass 252.3.

III. Claims 54-75, drawn to methods of desulfurizing fossil fuels using enzymes, microorganisms and transformed microorganisms, classified in class 435, subclass 282.

3. The inventions are distinct, each from the other because of the following reasons: Inventions I and II are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP § 806.04, MPEP § 808.01). In the instant case, the culture of Invention I and the transformed host cells of Invention II have different modes of operation. For example, the untransformed culture of Invention I produces enzymes for the biodesulfurization of fossil fuels encoded in the bacterial genome, whereas the transformed host cells of Invention II overexpress the desulfurization enzymes from an expression vector, under the control of a variety of exogenous (or endogenous) promoters.

Inventions I and III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the methods of desulfurizing fossil fuels of Invention III are not limited to the use of the *Sphingomonas* culture of Invention I. For example, the methods of Invention III can be practiced with transformed host cells and purified enzymes.

Inventions II and III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the methods of desulfurizing fossil fuels of Invention III are not limited to the use of the purified enzymes and transformed host cells of Invention II. For example, the methods of Invention III can be practiced with the untransformed *Sphingomonas* culture of Invention I.

4. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

5. During a telephone conversation with Ed Harlan on May 5, 1998, a provisional election was made **with traverse** to prosecute the invention of Group II, claims 2-53. Affirmation of this election

must be made by applicant in replying to this Office action. Claims 1 and 54-75 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

6. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(I).

Information Disclosure Statement

7. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Drawings

8. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claim 27, 28, 32, 33 and 38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The invention appears to employ novel microorganisms. Since the microorganisms are essential to the claimed invention, they must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The claimed microorganisms have not been disclosed to be publicly known and freely available. Accordingly, it is deemed that a deposit of these microorganisms should have been made in accordance with 37 CFR 1.801-1.809. The enablement requirements of 35 U.S.C. 112 may be satisfied by a deposit of the microorganisms.

It is noted that applicants have deposited, under the terms of the Budapest Treaty, the microorganisms of claim 38, but there is no indication in the specification as to public availability. (see instant specification, page 5, lines 15-20). An affidavit or declaration by applicants, or a statement by an attorney of record, over his or her signature and registration number, stating that the specific strain has been deposited under the Budapest Treaty **and** that the strain will be irrevocably and without restriction or condition released to the public upon the issuance of the patent, would satisfy the deposit requirement made herein.

11. Claims 2, 4, 6, 8, and 46-53 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 2, 4, 6, and 8 are drawn to nucleic acids encoding enzymes described by SEQ ID NO: 2, 4, and 6, **OR** nucleic acids encoding mutants, fragments or homologues of the enzymes described by SEQ ID NO: 2, 4, and 6. Claims 46-53 are drawn to vectors and transformed microorganisms comprising the nucleic acids encoding mutants, fragments or homologues of the enzymes described by SEQ ID NO: 2, 4, and 6.

The instant disclosure is enabling for claims limited to: 1) the nucleic acids described by SEQ ID NO: 1, 3, and 5, vectors and transformed host cells thereof; 2) nucleic acids encoding the polypeptides described by SEQ ID NO: 2, 4, and 6, vectors and transformed host cells thereof; 3) nucleic acids encoding enzymatically active fragments of the polypeptides described by SEQ ID NO: 2, 4, and 6, vectors and transformed host cells thereof, and 4) nucleic acids comprising at least 20, 40 or 50 contiguous nucleotides of the polynucleotides described by SEQ ID NO: 1, 3, and 5. The scope of the instant claims is not commensurate with the enablement of the instant disclosure, because practice of the claimed invention would require **undue** experimentation by an artisan of ordinary skill in the art. The instant specification is not enabling for claims drawn to nucleic acids encoding mutants, fragments or homologues of the polypeptides described by SEQ ID NO: 2, 4, and 6.

The factors to be considered in determining whether **undue** experimentation is required are summarized *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in *Wands*

states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In *Wands*, the determination that undue experimentation was not required to make the claimed invention was based primarily on the

nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (*Wands*, 8 USPQ2d 1406). Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of *Wands* factors which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

In the instant case, claims 2, 4, 6, 8, and 46-53 are broader than the enablement provided by the disclosure with regard to the extremely large number of nucleic acids, vectors and transformed host cells encoding mutants, fragments and homologues of the polypeptides described by SEQ ID NO: 2, 4, and 6. The enzymes described by SEQ ID NO: 2, 4, and 6, for example, consist of 453, 369 and 412 amino acids, respectively. Thus, the instant claims encompass all enzymes encoded by SEQ ID NO: 2, 4, and 6, in which up to all of the amino acids of each enzyme are modified to any of 20 natural protein amino acids. This corresponds to between at least 2×10^{370} and 2×10^{454} possible mutant enzymes, many of which will be inoperative (i.e. enzymatically inactive), which, because of the redundancy of the genetic code, are encoded by a multitude of nucleic acids. Thus, the number of embodiments of the instant claims is many orders of magnitude greater than the number of possible mutant enzymes. Although the synthesis and screening of between 2×10^{370} and 2×10^{454} polypeptides and the subsequent synthesis of the corresponding polynucleotides constitutes a considerable amount of experimentation, the instant specification does not disclose any specific amino

acid residues which may be modified to a mutant enzyme which retains enzymatic activity. The prior art does not teach designer, engineered desulfurization enzymes dszA, dszB and dszC from *Sphingomonas*. The difficulty of predicting the functional effects of random single amino acid substitutions is well known in the art. In discussing the relationship between particular amino acid substitutions and biological activity, Rudinger (U) states that "the significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study." (see page 7, conclusion). Although the state of the art has advanced significantly since the publication of Rudinger (U), these advances are primarily technical, enabling an artisan of ordinary skill in the art to produce nearly any mutant or variant protein in quantity. Rudinger (U) states merely that the effects of any one mutation, much less multiple mutations, on biological activity is unpredictable in the absence of additional experimentation relating the structure of the protein to its biological function. The relationship between the sequence of a peptide and its tertiary structure (i.e., its activity) are not well understood and are not easily predictable (see Ngo et al. (V)) and the state of the art is still such that a skilled artisan cannot predict biological function, *a priori*, from the protein primary structure. Thornton et al. (W) discuss the current state of the art of protein engineering. (see pages 367-369). Specifically, with regard to the unpredictability of relating a protein sequence to either its tertiary structure or biological or enzymatic activity, *a priori*, Thornton et al. (W) state:

> The Oxford dictionary definition of an engineer is one with expertise in design, construction and maintenance. The evidence to date shows that although we are still not very good at design--but learning and improving all the time--the experimental

> construction and maintenance of any protein sequence is now possible. The challenge is to design proteins with required structures and functions to use as tools in the laboratory and to benefit society in medicine, industry and agriculture. (see Thornton et al. (W), page 369, column 2, paragraph 1, lines 1-9).

Thus, the state of the art at the time the invention was made was such that one of ordinary skill in the art could produce any addition, deletion or substitution mutant, fragment or homologue of the enzymes described by SEQ ID NO: 2, 4, and 6, which, if combined with sufficient guidance to identify functionally relevant amino acid residues, would not constitute undue experimentation. In the absence of guidance relevant to structural or sequence homology information, either in the instant specification or prior art, it is nearly impossible to predict the functional effects of single amino acid substitutions, additions or deletions, much less substitutions, additions or deletions involving multiple amino acids. In addition to quantity of experimentation, guidance, relative skill of those in the art and the predictability or unpredictability of the art, as discussed in *Wands*, the nature of the invention is also an important factor. For example, the determination that undue experimentation was not required to make the claimed invention in *Wands* was based primarily on the nature of the invention. (*Wands*, 8 USPQ2d 1406). Although the nature of the monoclonal antibody technology discussed in *Wands* requires considerable screening of hybridomas, protein engineering is based on the relationship between the structure and function of a protein molecule and only requires limited screening of rationally engineered proteins which are based on functional and/or structural information, not large-scale screening of randomly generated proteins.

> Lately site-directed methods have opened up the possibility of engineering virtually any protein. There is, however, a danger that a 'shotgun' approach will prove

> wasteful of effort. Useful protein engineering requires careful consideration of informative substitutions... ." (see Wallace (X), page 514, column 1, paragraph 3, lines 5-11).

Thus, in view of the lack of working examples, lack of guidance in the specification and the prior art, the unpredictability and nature of the art of protein engineering and the great breadth of the claims, the expectation that one of ordinary skill in the art would successfully obtain the claimed invention without **undue** experimentation is extremely low.

In addition, in *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991), the court ruled that a claim to a large genus of possible genetic sequences encoding a protein with a particular function that needs to be determined subsequent to the construction of the genetic sequences may not find sufficient support under 35 U.S.C. 112, first paragraph, if only a few of the sequences that meet the functional limitations of the claim are disclosed, and if undue experimentation would be required of one skilled in the art for the determination of other genetic sequences that are embraced by the claim. This is the case here. In other words, since it would require undue experimentation to identify and isolate mutants, fragments and homologues of the enzymes described by SEQ ID NO: 2, 4, and 6, it certainly would require undue experimentation to make their corresponding DNA, vectors and transformed host cells. Therefore, the entire scope of claims 2, 4, 6, 8 and 46-53 is not enabled.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 3, 5, 7, and 24-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 3, 5, and 7 are drawn to nucleic acids having nucleotide sequences which are **substantially the same** as those described by SEQ ID NO: 1, 3, and 5, respectively. Claims 24-39 are drawn to enzymes having nucleotide sequences which are **substantially the same** as those described by SEQ ID NO: 2, 4, or 6. Recitation of "substantially the same" renders the claims vague and indefinite, because it is not clear at which point a nucleic acid or enzyme, when compared to a molecule described by SEQ ID NO: 1, 3, and 5, or SEQ ID NO: 2, 4, and 6, respectively, is **substantially not the same**. For example, two nucleic acid molecules which are **substantially the same** may differ by 0.5%, 1%, 10%, 50% or greater. Thus, claims 3, 5, 7, and 24-39 are indefinite. In the interest of compact prosecution, the claims have been treated on the merits.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 28, 34, and 39 are rejected under 35 U.S.C. 102(b) based upon a public use or sale of the invention. Claims 28, 34, and 39 are drawn to fragments, of any length of the polypeptides described by SEQ ID NO: 2, 4, and 6, respectively. The claims are not limited to fragments which

are enzymatically active. Thus, claims 28, 34, and 39 read on any of the 20 naturally occurring protein amino acid.

Sigma Chemical Company of St. Louis, Missouri (Y) sells L-glycine (Catalog No. G7403, page 502 1995 Sigma Catalog). Thus, the L-glycine sold by Sigma Chemical Co. (Y) anticipates the polypeptide fragments of claims 28, 34, and 39.

Conclusion

15. Claims 9-23 and 40-45 are allowable over the prior art of record. A diligent search of electronic patent and scientific literature data bases revealed no prior art teaching or suggesting the nucleic acids, vectors, transformed microorganisms, and purified polypeptides of the instant claims, claims 9-23 and 40-45.

16. The Group and Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1652.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Einar Stole, Ph.D., whose telephone number is (703) -305-4507. The examiner can normally be reached Tuesday through Friday 6:30 a.m. to 5:00 p.m.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Robert A. Wax, can be reached on (703)-308-4216. The fax phone number for Technology Center 1600 is (703)-305-7401.

Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703)-308-0196.

Einar Stole, Ph.D.

June 6, 1998

ROBERT A. WAX
SUPERVISORY PATENT EXAMINER
GROUP 1800/1650